

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

IN RE US PATENT APPLICATION OF

YIQING ZOU ET AL.

SERIAL NO. 08/216,440

FILED: MARCH 23, 1994

FOR: ANTIMALARIAL COMPOSITIONS

Commissioner of Patents and Trademarks

Washington D.C. 20231 USA

DECLARATION OF BONAN LIN

I, BONAN LIN, citizen of China, resident of Beijing China, do hereby declare and say as follows:

That I am a Graduate of The Tsinghua University, where I received in 1982 the Degree of Bachelor of Science (B.S.) in Chemical Engineering;

That I am now a Patent Attorney;

That I am presently employed in the Patent Agency of the China Council for the Promotion of International Trade;

That I am a member of the All China Patent Agent Association;

That I am knowledgeable in the English and Chinese languages;

That the publication according Chemical Abstracts 112: **48094s**, issued on Feb.12, 1990 (Exhibit 1), entitled Recent Progress in research on antimalarials in China, author: Deng, Rong-Xian, member of the Institute of Microbiology and Epidemiology in the Academy of Military Medical Sciences, published in Zhongguo Yiyao Gongye Zhazi 1989, 20 (8), 372-376, corresponds to the publication published in the Chinese Journal of Pharmaceuticals 1989, **20(8)**, pages 372-378 (Exhibit 2);

That in the Chinese Journal of Pharmaceuticals 1989, 20(8), only the paragraph on page 375, left column, lines 3-13 relates to artemether and benflumetol;

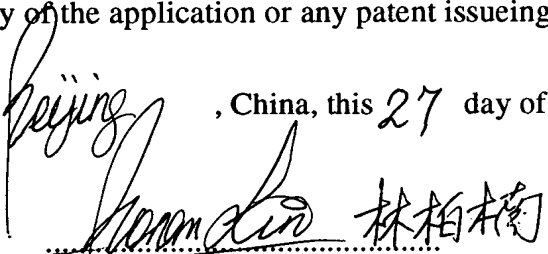
That the translation of this paragraph that appears most accurate is as follows:

The combination of artemether and benflumetol in proper proportions has synergistic action and possesses the advantage of both rapid action of artemether and thorough parasitocidal action of benflumetol, and also possibly retards the emergence of single drug resistance and reduces the dosage of single drugs. The toxicity of such combination is only additive.

To explore this, these two individual drugs were first administered simultaneously for treatment of falciparum malaria patients in endemic areas of chloroquine resistance in Hainan Province. The results demonstrated that the parasite clearance rate, fever subsidence rate and cure rate were all better than that of single drugs or chloroquine. The regimen was convenient and safe for use, and has entered clinical trial Phase II.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed at Beijing, China, this 27 day of July, 1994.


Bohan Lin

The following Exhibits are parts of this Declaration:

Exhibit 1: Chemical Abstracts 112: 48094s, issued on Feb.12, 1990.

Exhibit 2: Chinese Journal of Pharmaceuticals 1989, 20(8), pages 372-378;

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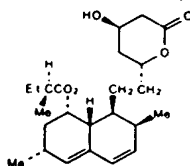
No. 7

1—PHARMACOLOGY

C. PAUL BIANCHI

This section includes the biochemical, physiological, and toxic effects of drugs or potential drugs, their metabolism, analysis in biological systems, and structure-activity relations. Drug formulations are included in Section 63; analysis of drug formulations appears in Section 64; the pharmacology of hormones and agents affecting reproduction, e.g., contraceptives, in Section 2; radiopharmaceuticals, in Section 8; effects of antibiotics, bactericides, etc., on microorganisms in vitro are placed in Section 10; studies emphasizing the synthesis of drugs are included in the appropriate synthetic organic or inorganic section; drugs used only as investigative or diagnostic tools appear in the section appropriate to the organism or process under investigation.

112:48092q New inhibitors of HMG-CoA reductase. Synthesis and structure-activity relationships. Baader, E.; Bartmann, W.; Beck, G.; Bergmann, A.; Jendralla, H.; Kessler, K.; Wess, G.; Schubert, W. (Hoechst A.-G., D-6230 Frankfurt, 80 Fed. Rep. Ger.). *Actual. Chim. Ther.* 1989, 16(Recontres Int. Chim. Ther., 24th, 1988), 133-42 (Eng). A review discussion, esp. of the author's work



with 21 refs. Modifications in the lactone part and replacement of the biaryl system of mevinolin (I) and its congeners, inhibitors of 3-hydroxy-3-methylglutaryl CoA reductase involved in their hypocholesteremic activity, was discussed.

112:48093r Effect of beta-receptor antagonists on metabolism. Gergely, Judith (Gyogyszertani Intez., Debreceni Orvostud. Egyet., 4012 Debrecen, Hung.). *Gyogyszereszet* 1989, 33(7), 345-7 (Hung). A review with 29 refs., with emphasis on the mechanism of action of beta-receptor-blocking drugs.

112:48094a Recent progress in research on antimalarials in China. Deng, Rongxian (Inst. Microbiol. Epidemiol., Acad. Mil. Med. Sci., Beijing, Peop. Rep. China 100071). *Zhongguo Yiyao Gongye Zazhi* 1989, 20(8), 372-6 (Ch). The recent progress in research on antimalarial drugs in China was reviewed, with 28 refs. Three new drugs and one prep. have been registered in China since 1985, including artemether, artesunate, benflumetol and Qinghaosu suppository. New drug naphthoquinone and combination of artemether-benflumetol are undergoing phase II clinic trials. Besides, the combination application of pyronaridine with other drugs has also been mentioned.

112:48095t Degradation of rat hepatic cytochrome P-450p. Correia, Maria Almira; Sugiyama, Katsumi; Yao, Kunquan (Liver Cent., Univ. California, San Francisco, CA 94143 USA). *Drug Metab. Rev.* 1989, 20(2-4), 615-28 (Eng). A review with 38 refs. on the mechanism of drug-mediated inactivation of dexamethasone-inducible isoenzymes of cytochrome P 450 (cytochrome P-450p) of liver microsomes, employing 3,5-dicarboxy-2,6-dimethyl-4-ethyl-1,4-dihydropyridine as the prototype inactivator.

112:48096u Blood platelet aggregation inhibitors from plants. Teng, Che Ming (Med. Coll., Natl. Taiwan Univ., Taipei, Taiwan). *Hua Hsueh* 1988, 46(4), 293-8 (Ch). A review with 32 refs. on platelet aggregation inhibitors from plants, structures of the compds., and classification of the compds. into 4 groups: receptor antagonists; inhibitors of phosphoinositol metab; inhibitors of prostanoic biosynthesis; and calcium antagonists.

112:48097v Recent developments on Ta Huang. Hsu, Hung Yuan (Taiwan Pi An Inst., Taiwan). *Hua Hsueh* 1988, 46(4), 303-10 (Ch). A review with 10 refs. on Ta Huang (a herbal medicine made from plants of the genera *Rheum* and *Rumex*), biol. active (diuretic, antispasmodic, antitumor, antihistamine, anticholine, and antiserotonin) compds. from Ta Huang, and structures of these compds.

112:48098w Mechanisms of antigen formation by interaction of drugs with cell membranes. De Weck, A. L. (Inst. Klin. Immunol., Inselspital Bern, 3010 Bern, Switz.). *Symp. Med. Hoechst* 1987 (Pub. 1988). 22(Toxicol. Immunol. Aspects Drug Metab. Environ. Chem.), 199-209 (Eng). A review with 13 refs. Expts. performed with lymphocytes from penicillin-allergic patients have revealed that the covalent binding of haptenic groups to membrane proteins of antigen presenting cells, followed by appropriate presentation in which MHC determinants are also involved, is the mechanism most likely to be stimulating for drug-specific T cells in culture. For most drugs, this step has to be preceded by metab. in culture mimicking in vivo conditions. Expts. performed on haptenated

mouse lymphoid cells under controlled MHC restriction conditions may confirm these conclusions, and provide diagnostic tests for drug allergy.

112:48099x Aspirin and human platelets: from clinical trials to acetylation of cyclooxygenase and back. Patrono, Carlo (Sch. Med., Catholic Univ., 00168 Rome, Italy). *Trends Pharmacol. Sci.* 1989, 10(11), 453-9 (Eng). A review with 24 refs. Aspirin has been convincingly shown to reduce the incidence of vascular occlusive events in a wide range of patients at risk of thrombotic complications. These beneficial effects are currently linked to suppression of thromboxane A₂-dependent platelet aggregation. This in turn reflects permanent loss of the cyclooxygenase activity of platelet prostaglandin G/H synthase, through acetylation of Ser530. Progress in the understanding of the mol. mechanism of action of aspirin and definition of the clin. pharmacol. of its platelet effects has been assoc. with a downward trend in its daily dosage. This has been reduced by a factor of 10 over the last decade, substantially reducing gastrointestinal toxicity, while leaving antithrombotic efficacy virtually unchanged.

112:48100r New antidepressants and 5-HT uptake inhibitors. Montgomery, Stuart A. (Med. Sch., St. Mary's Hosp., London, UK W2 1NY). *Acta Psychiatr. Scand., Suppl.* 1989, 350, 107-16 (Eng). A review with 59 refs. The efficacy of 5-HT uptake inhibitors, including paroxetine, as antidepressants is compared with that of the ref. tricyclic antidepressants.

112:48101s Pharmacokinetic implications for the clinical use of propofol. Kanto, Jussi; Gepts, E. (Dep. Anaesthesiol., Univ. Turku, SF-20520 Turku, Finland). *Clin. Pharmacokinet.* 1989, 17(5), 308-26 (Eng). A review with 57 refs. Anal. methods for and pharmacokinetic properties of propofol as anesthetic, along with effect of age, gender, obesity, various pathophysiol. states and type of surgical procedure, pharmacokinetic interactions, infusion kinetics, etc., are discussed.

112:48102t Drug interactions involving aspirin (acetylsalicylic acid) and salicylic acid. Miners, John O. (Dep. Clin. Pharmacol., Flinders Med. Cent., Adelaide, 5042 Australia). *Clin. Pharmacokinet.* 1989, 17(5), 327-44 (Eng). A review with many refs. Salicylate disposition, drug interactions involving aspirin and salicylic acid, and non-interactions with these 2 drugs are discussed.

112:48103u Amethopterin metabolism in mammalian cells. Balinska, Malgorzata (Inst. Biol. Dosw. im. M. Nenckiego, PAN, 02-093 Warsaw, Pol.). *Postepy Biochem.* 1988, 34(4), 417-27 (Pol). A review with 69 refs. on the metab. and pharmacol. of amethopterin (methotrexate) and its metabolite 7-hydroxymethopterin in normal and neoplastic cells.

112:48104v *Eleutherococcus senticosus* on the way to becoming a pharmacognostic product. Sprecher, Ewald (D-2000 Hamburg, 56 Fed. Rep. Ger.). *Pharm. Ztg.* 1989, 134(45), 9-10, 13-14, 16-17 (Ger). A review, with 26 refs., discussing the occurrence of the ginseng-related plant *E. senticosus*, its root compn. (eleutherosides, phenylpropane derivs., coumarins, etc.), its "adaptogenic" effect, i.e. its stressor-specific effects, whereby deviating body functions are returned to the physiol. norm irresp. of the direction required (inhibiting or promoting), theories concerning the mechanism of this, and its immunostimulatory properties.

112:48105w Ketoconazole, a new imidazole antifungal agent. Liu, Gaolin; Gao, Shen (2nd Mil. Med. Coll., Shanghai Hosp., Shanghai, Peop. Rep. China). *Zhongguo Yaowu Zazhi* 1989, 24(5), 267-70 (Ch). A review, with 34 refs., of the pharmacol., pharmacokinetics, toxicity, and clin. uses of ketoconazole as an antifungal agent.

112:48106x Levodopa drug interactions. Tong, Chengshu (Liaoyang Petrofiber Co. Hosp., Liaoyang, Peop. Rep. China). *Zhongguo Yaowu Zazhi* 1989, 24(5), 307-8 (Ch). A review, with 11 refs., of levodopa drug interactions in the treatment of parkinsonism.

112:48107y Research progress in angiotensin-converting enzyme inhibitors. Li, Kai (Dep. Pharmacol., Hunan Med. Coll., Changsha, Peop. Rep. China). *Zhongguo Yaowu Zazhi* 1989, 24(5), 259-62 (Ch). A review, with 31 refs., of the development and clin. pharmacol. of angiotensin-converting enzyme inhibitors.

综述

我国近几年抗疟药研究新进展

邓 蓉 仙

(军事医学科学院微生物流行病学研究所, 北京 100071)

摘要 综述了我国抗疟药研究的新进展。自 1985 年以来有三种新药和一种制剂在国内注册, 它们是: 蒿甲醚、青蒿琥酯、本茆醇和青蒿素栓剂; 新药萘酚喹和蒿甲醚-本茆醇复方正进行第 II 期临床试验。此外, 咯萘啶与其他药物伍用亦取得进展。

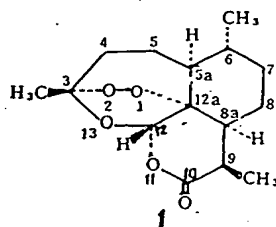
关键词 抗疟药 蒿甲醚 青蒿琥酯 本茆醇 复方

疟疾至今仍在全世界广泛流行, 60 年代初恶性疟原虫对主要抗疟药氯喹产生了抗药性, 抗氯喹恶性疟不断扩散蔓延, 已遍及亚洲、美洲、大洋洲和非洲等许多地区, 我国海南、云南、广西等省的某些地区也有流行。且抗药性的程度不断增加, 从单药抗药性向多药抗药性发展, 已成为当前世界医学和公共卫生急待解决的一个严峻问题, 引起了高度重视。世界卫生组织(WHO)成立了专门机构, 制订了长远的研究规划, 并组织庞大科研队伍寻找与氯喹无交叉抗药性的新抗疟药。我国在 60 年代后期也组织了全国性的新抗疟药研究, 经过廿多年的努力, 取得了显著成绩, 研制出一批新抗疟药, 如青蒿素、喹啉及其类似物羟基喹啉、咯萘啶及其类似物咯啉、常咯啉以及硝喹、脑疟佳等, 还组成了几个新药的复方, 其中部分药物已广泛使用, 对控制我国疟疾流行作出了贡献。有关我国抗疟药研究的情况已有综述^[2,3]。本文仅就 1985 年以后获得卫生部颁发的新药证书, 以及经新药审批委员会批准进入 II 期临床试验的新药作一简要介绍。

一、青蒿素栓剂

在确定青蒿素结构和绝对构型的基础上, 青蒿素(I)已成功地实现了全合成^[4]。它的化学名为: (+)-八氢-3, 6, 9-三甲基-3, 12-环氧-12 H-吡喃并[4, 3-j]-1, 2-苯并二

噁庚英-10(3 H)-酮[3 R-(3 α , 5 α , 6 β , 8 α , 9 α , 12 β , 12 α R)]。



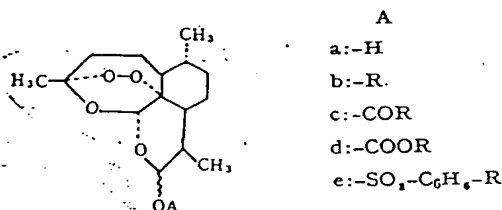
青蒿素在水和油中的溶解度均小, 难以制成实用的制剂, 口服的剂量偏大, 最后制成栓剂直肠给药。青蒿素栓剂采用水、生基质, 临床药物动力学研究表明, 直肠给药后 10~11 h 血浆浓度达峰值, 从血液中消除的半衰期为 4 h。临床上成人治疗的总剂量为 2.8 g, 采用三日六次疗法, 每日给药 2 次, d1 每次 600 mg, 间隔 4 h, d2 及 d3 每次 400 mg, 间隔 8 h, 对各类疟疾均能迅速控制临床症状, 使原虫转阴。治疗 355 例恶性疟, 退热需 15~39 h, 原虫转阴需 36~53 h, 经 28 天随访, 83 例的复燃率为 45.8%; 治疗 58 例间日疟, 退热平均需 16 h, 原虫转阴平均需 32 h; 治疗 24 例脑型疟, 退热和原虫转阴分别需 36 和 57 h, 病人从昏迷到恢复意识约需 22 h, 治愈率为 91.7%。不良反应包括里急后重(5.9%)、腹痛(3.1%)和腹泻(0.8%), 均属

一过性。

青蒿素栓剂的优点是不需要注射, 使用方便, 对成人、儿童和昏迷病人, 均可应用, 尤适宜于农村和边远地区的病人, 已由广州白云山制药厂生产。

二、青蒿素的衍生物

为了克服青蒿素溶解度小的缺点, 加大脂溶性或水溶性, 合成了具有抗疟活性的二氢青蒿素的醚类、羧酸酯类、碳酸酯类和磺酸酯类, 以及含杂原子的衍生物 150 多个(2)。这些衍生物多具油性, 其二元酸单酯的钠盐具水溶性, 它们的抗鼠疟作用均明显优于青蒿素^[5-10]。



1. 二氢青蒿素(dihydroartemisinin, 2a)

二氢青蒿素又称还原青蒿素, 是将青蒿素用硼氢化钠还原而制得, 也是青蒿素类化合物在体内的有效代谢产物^[11, 12], 其抗鼠疟(*P. berghei*)活性比青蒿素强一倍。已进入Ⅱ期临床试验。

2. 蒿甲醚(artemether, 2b, R=Me)

蒿甲醚的 10 位 OCH₃ 具 β-构型, 又称 β-甲基二氢青蒿素, 对疟原虫红细胞内期裂殖体有很强的杀灭作用, 与氯喹几无交叉抗性(抗性指数为 1.7), 对伯氏鼠疟原虫耐氯喹株的 ED₅₀ 为 1.0 mg/kg, 比青蒿素(ED₅₀ 为 6.2 mg/kg)强 5 倍, 使猴疟(*P. cynomolgi*)转阴的最低剂量为 3 mg/kg, 作用迅速, 一天内原虫可减少 90% 以上, 两天内全部清除。毒性比青蒿素稍低, 小鼠肌注蒿甲醚和青蒿素油剂的 LD₅₀ 分别为 274 和 217 mg/kg^[13]。动物药理学试验表明, 兔肌注蒿甲醚的吸收率为 35%^[14], 药物在小鼠体内

的生物转化过程是 OCH₃ 脱去甲基, 约占给药量的 31%; 动物实验表明, 肌注给药比灌胃疗效高, 故制成蒿甲醚的花生油(1 ml 含 80 mg)注射剂在临床应用; 人体肌注蒿甲醚 10 mg/kg 后血药达峰时间为 7.3 h, 峰值为 0.8 μg/ml, 血浆半衰期为 13.2 h。

曾用蒿甲醚注射剂的多种给药方案治疗现症疟疾数千例, 包括恶性疟、间日疟、凶险型疟疾和妊娠妇女等, 均获满意的结果^[15-17]。最后选用的给药方案是每天肌注 80 mg 一次, 首次加倍, 连续 5 天, 总剂量 480 mg, 在海南和云南抗氯喹恶性疟流行地区治疗恶性疟 278 例, 包括凶险型 13 例, 孕妇 2 例, 全部临床治愈, 退热时间需 20~29 h, 原虫转阴时间需 54~76 h, 对其中的 241 例追踪观察 28 天, 复燃率为 7.1%, 明显低于青蒿素。其副反应轻微, 病人体温恢复后偶见短暂升高(3%), 偶见网织红细胞下降至略低于正常的低限值, 但易恢复。本品已由昆明制药厂生产。

3. 青蒿琥酯(artesunate, 2c, R=-(CH₂)₂COOH)^[5, 10, 17]

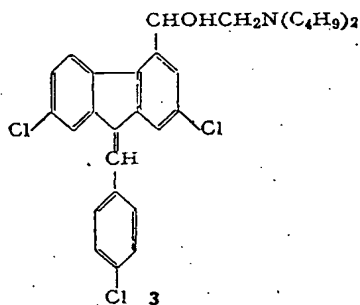
青蒿琥酯 10 位的琥珀酸单酯基为 α-构型, 又称二氢青蒿素-α-琥珀酸单酯。青蒿琥酯的游离酸为无色结晶性粉末, 在水中溶解度极低, 其钠盐的水溶液不稳定, 可分解为二氢青蒿素和琥珀酸。因此, 制成双包装粉针剂型, 临用时将青蒿琥酯溶解在 5% 的 NaHCO₃ 溶液中, 供静脉注射。静注青蒿琥酯对鼠疟正常株的疗效与静注氯喹相当, 杀虫速度比氯喹快, 与氯喹仅有轻微的交叉抗性; 对猴疟(*P. knowlesi*)的疗效和杀虫速度明显优于二盐酸奎宁。对小鼠的 LD₅₀ 为 769 mg/kg(静注), 化疗指数为 793; 对狗的毒性不大, 有效剂量与安全剂量相差较大; 对雄性大鼠生殖功能似无影响, 但雌性大鼠于受孕中期给药, 有明显的胚胎毒性。药物动力学研究^[18, 19]表明静注后兔血药浓度半衰期为 12~23 min, 狗为 20~33 min, 人体血

的最低治愈剂量分别为 48 和 12 mg/kg × 7 d。本苋醇的毒性极低, 小鼠、大鼠口服单剂量 10 g/kg, 小鼠皮下注射 5 g/kg, 观察二周, 无中毒表现; 亚急性毒性的安全剂量, 大鼠为 250 mg/kg 连服 90 d, 狗为 240 mg/kg 连服 28 d, 致死剂量未能测出, 大鼠和狗分别口服本苋醇 1 g/kg 连续 90 d 和 480 mg/kg 连续 28 d, 均无死亡。

本苄醇在水和油中都不溶解，而易溶于不饱和脂肪酸如油酸和亚油酸中⁽²⁾，故制成亚油酸胶丸剂型在临床应用。临床药物动力学研究表明：血浆浓度-时间曲线符合二室开放模型，它在健康成人体的终末相半衰期($t_{1/2\beta}$)为 47.4 h，半吸收期($t_{1/2k_a}$)和半分布期($t_{1/2\alpha}$)分别为 3.6 和 1.6 h。药物在体内吸收较慢，分布较快，消除较慢。口服单剂量 800 mg 后 1.5 h，药物开始在血浆中出现，5 h 左右达峰值，再缓慢下降，150 h 后仍能被检出；按临床(总剂量 2 g)用药方案分次口服后，血浆能维持较高的药物浓度，96 h 内的平均值约为 5760.85 ng/ml。

蒿乙醚 (arteether, $2_dR=Et$) 为我国学者首先合成, 并发现它对鼠疟抗氯喹原虫株的作用比青蒿素强^[6]。现由 WHO 疟疾化疗工作组在国外开发, 由 TDR 和 WRAIR 等机构协作研制肌注剂型^[20]。

化学名为 β -二丁胺基-[2, 7-二氯-9-(对氯苯亚甲基)-4-苄]乙醇, 是我国创制的一种治疗恶性疟的新药, 对伯氏鼠疟原虫正常株有显著疗效, ED_{50} 和 ED_{90} 分别为 1.02 和 2.04 mg/kg \times 4 d, 略优于氯喹和甲氟



用本苄醇胶丸在海南和云南抗氯喹恶性疟流行地区以多种方案治疗恶性疟 597 例, 均获满意的结果^[21]。最后选定 2 g、d 方案(首次 800 mg, 以后每日一次 400 mg)治疗 314 例恶性疟, 全部临床治愈, 随访 23 d 的复燃率为 4.5%。而用氯喹对照治疗的 89 例, 未能全部临床治愈, 复燃率高达 69.7%; 治疗 14 例临床确证为抗药性的恶性疟(9 例抗氯喹, 5 例为多价抗药性), 全部临床治愈, 平均退热时间为 34.1 h, 平均原虫转阴时间为 56.6 h, 随访 28 d 无复燃。说明本苄醇对抗氯喹恶性疟有很好的疗效, 平均治愈率达 95% 以上; 与文献^[23~25]报道的甲氟喹 1.5 g 或卤泛群(halofantrine)500 mg 每 6 h 一次, 共给药三次的治愈率相当。但毒副反应远比后二者为低, 据文献报道, 服甲氟喹的病人约有 10~40% 出现腹泻、腹痛、呕吐、头晕, 服卤泛群的病人亦出现类似的反应。毒

副反应低是本药醇的优点。本品已由昆明制药厂生产。

四、蒿甲醚和本药醇复方

蒿甲醚和本药醇按合适比例组成复方时具有协同作用,该复方兼具蒿甲醚速效和本药醇杀虫彻底的优点,又能延缓单药抗药性的产生,并可减少用量,复方的毒性仅具相加作用。

初步以联合用药的方式,在海南抗氯喹恶性疟流行地区,治疗恶性疟疾病人,其杀虫、退热的速度和治愈率均明显优于单药和氯喹,使用方便、安全,已进入Ⅱ期临床试验。

五、咯萘啶(pyronaridine)配伍

咯萘啶于1975年鉴定,是我国创制的新抗疟药,为了增加疗效、降低复燃率、防止抗药性产生,用咯萘啶(PND)与磺胺多辛(周效磺胺S)和乙胺嘧啶(P)进行配伍。配伍后具有增效作用,并能延缓抗药性产生。用PND/S/P(1200/500/25 mg)二日疗法,对恶性疟有满意的疗效,复燃率比单药明显降低^[26];用PND/S/P(500/1500/75 mg)一次顿服治疗恶性疟,能快速控制症状,使原虫消失,随访28 d无复燃^[27]。另据报道,用PND/伯氨喹配伍3 d疗法根治间日疟,效果与氯喹/伯氨喹8天疗法相当^[28]。

六、萘酚喹(naphthoquine)

萘酚喹是我国创制的一种新抗疟药,动物实验表明,它对鼠疟(*P. berghei*)、猴疟(*P. cynomolgi*和*P. knowlesi*)均具有高效、速效、长效抗疟作用。已进入Ⅱ期临床试验,初步结果令人满意。

廿多年来,我国新抗疟药研究形成了一支配套的、综合性的科研队伍,已从仿制和老药配方发展到研制出十多个新药和复方,这与我国抗疟工作者艰苦努力和大协作精神是分不开的。我国抗疟药研究的成果引起了全世界的极大关注。WHO疟疾化疗科研工作组会议1981年在我国举行之后,今年4月又

一次在北京召开,说明我国的抗疟药研究在国际上占有一定的地位。与会的各国代表对中国抗疟药研究的新进展给与了高度评价。

但我国抗疟药研究的发展尚不平衡,已研制出的新药多属治疗药、急救药和抑制性长效预防药;病因性预防药品种不多,间日疟根治药还是空白,急待研究解决,任务十分艰巨。

我国是一个疟疾流行的国家,近年来发病率虽有下降,但疫情尚不稳定,稍不注意就会回升,甚至出现暴发流行。疟疾又与战争是一对孪生兄弟。因此,从保护全人类生命健康、保障我国社会主义建设和巩固国防的需要出发,切不可放松新抗疟药的研究。

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RECENT PROGRESS IN RESEARCH ON ANTIMALARIALS IN CHINA

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ABSTRACT The recent progress in research on antimalarial drugs in China has been described. Three new drugs and one preparation have been registered in China since 1985, including artemether, artesunate, benflumetol and Qinghaosu suppository. New drug naphthoquine and combination of artemether-benflumetol are undergoing phase II clinic trails. Besides, the combinative application of pyronaridine with other drugs has also been mentioned.

Key Words antimalarials, artemether, artesunate, benflumetol, combination

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氟代嘧啶类抗肿瘤药物及其合成工艺进展

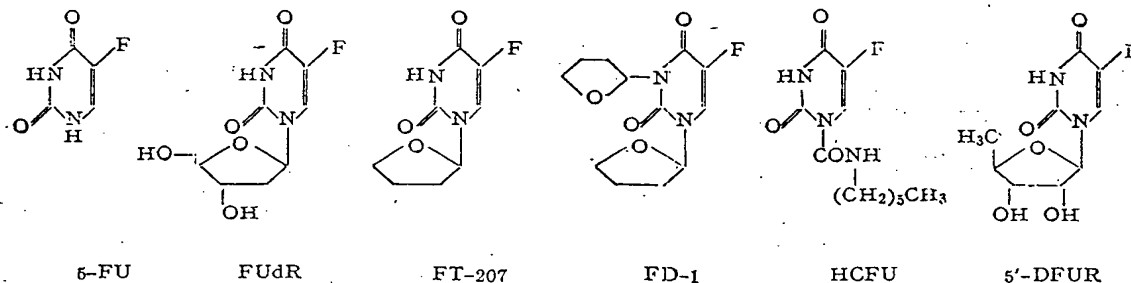
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摘要 对目前临床上最常用的一类抗肿瘤药物氟代嘧啶类抗代谢物的研究进展和某些主要药物的合成工艺改进进行了简述。

关键词 氟代嘧啶 抗肿瘤药物 合成

氟代嘧啶类抗代谢物是目前临床上最常用的一类抗肿瘤药物, 对上皮组织的实体瘤如腺癌等有效, 能与烷化剂、抗肿瘤抗生素和其它抗代谢抗肿瘤药物合用, 可供口服、静脉和动脉或腔内注射、外用和直肠给药。已上市的品种有: 5-氟尿嘧啶(5-FU), 氟苷(FUdR), 喃氟啶(FT-207), 双喃氟啶(FD-1), 己氨甲酰氟尿嘧啶(HCFU)和5'-脱氧氟尿嘧啶核苷(5'-DFUR)。结构式如下:



一、氟代嘧啶类抗肿瘤药物研究进展

由于氟原子半径及空间体积与氢原子非常接近,可满足酶对底物的空间要求,又碳-氟键与碳-氢键的性质差别甚大(如电负性、键能等),因而在有机化合物分子中引入氟原子常能获得具有显著生物效应的新化合物。Duschinsky 等于 1957 年在尿嘧啶的 5 位引入氟原子合成了 5-FU^[1],并预示它由于其稳定的碳氟键结构和酸性的增强能更牢固地与酶结合,可能代替肿瘤核酸的重要前体尿嘧啶参入 RNA,也可阻断尿嘧啶 5 位的甲基化而抑制 DNA 的合成,从而发挥抗肿瘤作用^[2]。药理和临床证实了其对实体肿瘤的疗效,于是 5-FU 成为第一个对消化道实体瘤有效的药物。

但 5-FU 的首过代谢显著及低亲脂性使其口服吸收不完全,直肠给药吸收更差,影响其抗肿瘤疗效。因此为提高 5-FU 的生物利用度,研制了所谓前体药物,设想通过其衍生物减少首过代谢,增强亲脂性^[3,4]。各国先后合成了大量的 5-FU 衍生物,特别是 N¹, N³ 的各种取代物,经药理、临床研究,筛选出较母体药物疗效更佳、毒性更低的前体药物如 FT-207, FD-1, HCFU, 5'-DFUR 等。

FT-207 是第一个研究成功的 5-FU 前体药物,由苏联的 Гиллер 于 1966 年首先合成^[5],经日本和苏联合作进行临床研究后,1974 年在日本上市。它用于口服、注射或直肠给药均易吸收,进入体内主要在肝脏内转化为 5-FU 而发挥抗肿瘤作用。因其能连续不断地释放出小剂量的 5-FU,使毒副反应大大下降,急性毒性仅为 5-FU 的 1/4~1/6,化疗指数要高出 2 倍左右。FT-207 剂型多样,有胶囊、片剂、栓剂、针剂、肠溶颗粒剂和细粒剂等,提供了不同的给药途径。对胃肠道肿瘤、乳腺癌、肺腺癌等有效,适用于合并治疗和维持治疗。

FD-1 是日本安本三治等于 1975 年首先合成的 FU 衍生物^[6]。动物实验结果表明:与 FT-207 相比,口服后在血和组织中达到的 5-FU 浓度要高 5~7 倍,在肿瘤组织中 5-FU 浓度尤高,为 8~12 倍,且维持时间较长;急性毒性仅为 FT-207 的 1/3^[7]。

生化研究已阐明 FD-1 在体内是通过 1 或 3-四氢呋喃基氟尿嘧啶代谢为 5-FU 的,其中代谢产物 3-四氢呋喃基氟尿嘧啶的抑瘤率高于 FD-1 和 FT-207^[8]。FD-1 在我国首先上市,对胃肠道肿瘤和原发性肝癌有效。

HCFU 是 1976 年由日本国立癌症研究所 Hoshi 等从一系列 1-烷基氨甲酰-5-氟尿嘧啶中筛选出来的 5-FU 前体药物^[9],具有广谱的抗肿瘤活性,不仅对发展迅速的动物肿瘤如白血病等,而且对生长缓慢的肿瘤如 Lewis 肺癌, B₁₆ 黑色素瘤等都有抑制作用,它与 FT-207 不同,对体外培养的肿瘤细胞也有活性。体内的代谢产物具有抗癌活性。口服后药物血浆浓度维持时间长,在癌性胸腹水中活性代谢物 5-FU 的浓度高^[10]。日本于 1981 年上市,它对胃癌、大肠癌和乳腺癌等有较好疗效,特别对浆膜腔积液疗效突出。

用氟原子取代 DNA 生化代谢物 2'-脱氧尿嘧啶核苷的 5-位氢原子所得的 FUDR,具有毒性低等优点,在肿瘤临床上治疗肝癌有效。体外的抗肿瘤活性大于 5-FU,但体内由于快速代谢为 5-FU 和易于随尿排泄等,疗效与 5-FU 相近。通常具有生理活性的核苷需要有 5'-羟基存在,在体内被磷酸化而发挥作用,如果去除 5'-羟基,将提供生化与生理研究饶有兴趣的化合物。由于它不能被磷酸化而参入核酸,可减少毒性,增加选择性。故而合成了许多 5'-脱氧核苷化合物提供药理筛选,其中 5'-脱氧-5-氟尿嘧啶核苷(5'-DFUR)对动物移植性肿瘤的疗效优于 5-FU、FT-207 和 FUDR,而免疫抑制毒性则仅为 FUDR 的 1/5 左右^[11]。5'-DFUR 口服后从胃肠吸收良好,体内在尿嘧啶核苷磷酸化酶(动物)或胸腺嘧啶核苷磷酸化酶(人)的作